

## **REMARKS**

Claims 23 and 27-49 are all the claims pending in the instant application. Applicant has amended claim 23 to better capture the envisioned commercial embodiments. Support for the claim amendments can be found throughout the original specification and claims as originally filed, at least in original claim 23. Accordingly, the amendments do not add new matter.

Applicants thank the Examiners for the courtesies extended and the helpful assistance provided during the personal interview of April 11, 2011. A summary of the substance discussed during the interview is incorporated into the remarks as set forth below.

### **Claims 23 and 27-49 Define Allowable Subject Matter**

A. Claims 23, 27-31, 36, 38-40 and 42-46 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Marler *et al.*, *Plast. Reconstr. Surg.*, 105:2049-2058 (2000) (“Marler”), in view of Bent *et al.*, *Neurobiology and Urodynamics*, 20:157-165 (2001) (“Bent”), Kuo *et al.*, *Biomaterials*, 22: 511-521 (2001) (“Kuo”), and Vanderhoff *et al.*, (WO 1996/39464) (“Vanderhoff”).

B. Claims 32-35, 37, 41 and 47-49 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Marler, Bent, Kuo, Vanderhoff, Grandolfo *et al.*, *Calcified Tissue International*, 52: 42-48 (1993), and Wong *et al.*, *Alginates in Tissue Engineering*, 238: 77-86 (2003).

As discussed in the April 11th Interview, as agreed upon by the Examiners, Applicants have amended claim 23 to specify that the injection of the pre-crosslinked alginate composition results in an increased tissue volume. Claim 23 as amended clearly distinguishes over the cited references for the reasons set forth below.

The Office alleges that “Marler teaches that a volume of 88% could be maintained over eight weeks using calcium alginate for tissue augmentation,” and “[a]ccording to Marler crosslinking of alginate gel is known to be done before and after injection of the alginate,” and concludes that Marler does not deter one of ordinary skill in the art from using fully crosslinked alginate gel. Page 8, *Office Action of 12 May 2010*. Applicants, however, respectfully note that

the Marler's disclosure regarding the 88% maintenance is only with respect to its construct "when it was crosslinked after rather than before injection." Second paragraph, Left Column, Page 2056 of Marler. Further, with respect to its construct crosslinked before injection, Marler (page 2053) shows that a pre-gelled alginate injection retains only about 30% of its volume 8 weeks post-injection. Accordingly, Applicants submit that Marler indeed deters one of ordinary skill in the art from injecting the fully-crosslinked alginates as recited in present claims.

Moreover, in response to Applicants' previous arguments that Kuo also teaches away from fully crosslinked alginates, the Office fails to address these arguments. *See* Page 9, Second full paragraph, *Office Action of 12 May 2010*. As discussed in the previous Amendment of November 12, 2011, Kuo's hydrogel, due to the slow crosslinking system, essentially contains un-crosslinked alginate particles. In particular, Kuo teaches a slow cross-linking system so that the "system would allow hydrogels to be injected into the body at a specific site, or being molded into any complex geometry before gelation occurs" Right column, page 517 (emphasis added). Accordingly, Kuo also teaches away from fully-crosslinking alginate before injection as recited in present claims.

Furthermore, Bent or Vanderhoff fails to cure the deficiency of Marler and Kuo because Bent and Vanderhoff are silent regarding any fully-crosslinking alginate before injection. In addition, Bent also teaches away from the presently claimed invention as Bent's pre-gelled alginate actually degrades. Accordingly, one of ordinary skill in the art would be deterred from adopting Bent's alginate to increase tissue volume as claimed in the present application.

For the reasons set forth above, Applicants submit that the collection of the cited references as a whole teaches away from combining the references to reach the presently claimed invention and thus would not motivate one of ordinary skill in the art to inject a composition comprising microparticles that are fully-crosslinked prior to injection as recited in claim 23.

In addition, Applicants respectfully assert that the rest of the rejected claims are allowable over the cited references at least because of their dependency from independent claim 23 and the reasons set forth above.

Accordingly, Applicants respectfully submit that the claims are not rendered obvious by the cited references and request that this rejection under 35 U.S.C. § 103 be reconsidered and withdrawn.

During the interview, the Examiners requested evidence that the microparticles prepared as shown in Example 3 of the present invention are “fully-crosslinked” to provide written support for the present claims. In response, Applicants file herein a Declaration signed by inventors showing that the microparticles according to Example 3 are fully-crosslinked in view of the excess divalent counter ions in the crosslinking solution which diffuse rapidly into the alginate beads. Specifically, all guluronic acids (23  $\mu\text{mol}$ ) in the alginate beads of Example 3 are fully-crosslinked by barium ions (2.2  $\mu\text{mol}$ ) forming egg box structures and calcium ions (12  $\mu\text{mol}$ ) linking two alginates. Accordingly, the microparticles prepared as shown in Example 3 of the present invention are indeed “fully-crosslinked,” and thus the originally filed specification has sufficient inherent support for the recited “fully-crosslinked” microparticles.

Should the Examiner believe that further discussion of any remaining issues would advance the prosecution, he or she is invited to contact the undersigned at the telephone number listed below.

Respectfully submitted,

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